INFLUENCE OF IRRADIATION ON RESISTANCE TO INFECTION

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The following tissue damage has been described after whole body X-radiation: destruction of the intestinal mucosal lining with ulceration and hemorrhage, destruction of lymphoid tissue and of bone marrow, severe leucopenia and thrombocytopenia, and damage to capillary endothelium (1, 2). The observations on germfree animals by Gordon and Scruggs at the Lobound Institute have shown that if the radiation damage is sufficiently severe death will ensue in the absence of complicating infection (3). Germfree rats, however, survive lethal doses of X-radiation significantly longer than conventional animals. Animals and men do not live in a germfree environment, and it is now well established that infection as a consequence of weakened defenses is a very frequent lethal complication of whole body X-radiation in the LD_{50} to LD_{100} range of dosage.

In atomic bomb casualties (1), after the second week, heavily infected ulcerated lesions in the skin, mucous membranes, and respiratory tract were observed, and there was also in some instances morphologic evidence of generalization of the infection with masses of bacteria in internal organs. Also in mice (4, 5), rats, and dogs (6), evidence of generalized infection has been reported following X-radiation. Most of the studies have been performed in mice. During the second week after irradiation with 450 to 600 r, the period of greatest mortality, overwhelming bacteremia was present in a large number of mice (4, 5). Miller and his group found 85 per cent of positive blood cultures in mice receiving 600 r; every mouse with bacteremia died. The organisms recovered were all members of the normal intestinal flora of mice (5, 7). The time between onset of bacteremia and death varied with the organism; *Pseudomonas aeruginosa* bacteremia was fatal in 24 hr, paracolon bacteremia in 4 to 5 days, and *Escherichia coli* and *Proteus* bacteremia in 48 to 72 hr (8).

The importance of intercurrent infection as a complication of X-radiation damage is further revealed by the favorable effects of antibiotics on this syndrome. Mice (9, 10), rats (11), and dogs (12) all show definite improvement in survival time when treated with antibiotics. The best results on mortality rate have been obtained in mice. Miller and associates (9, 13) observed that streptomycin in the optimal dose of 5 mg per day was the most effective agent, although oral antibiotics also gave good results. Mortality after 450 r was reduced by streptomycin therapy from 84 per cent in controls to 30 per cent in the treated mice (9).

Besides spontaneous infections, mice that have received 400 to 600 r of whole body X-radiation are also more susceptible to experimentally induced infections with doses of microorganisms which are not lethal for the normal animal (14). Kaplan *et al.* (15) infected mice intramuscularly with hemolytic streptococci 1 to 3 days after exposure to an LD_{50} of X-radiation. The infected animals died as the streptococci spread from the local lymph nodes to the liver, spleen, and blood by the 5th day of the infection. De Gara and Furth (16) reported that 300 r given 24 to 48 hr before intranasal infection significantly increased the susceptibility of mice to small doses of pneumotropic viruses.

Shechmeister *et al.* (17) studied the susceptibility of mice to graded doses of airborne *Streptococcus zooepidemicus* over a 50-day period following 350 r whole body X-radiation, in an attempt to see whether a chronological relationship existed between the increased susceptibility to infection and damage to various cellular systems. Susceptibility showed a linear increase in the first 15 days followed by an exponential drop to 30 days. Hammond and associates (18) made a similar study of the susceptibility of irradiated mice to fatal infection with *Pseudomonas aeruginosa* after oral inoculation of the organism in doses which had been found harmless for normal mice. Rapid death occurred most frequently among mice inoculated on the 11th day after radiation, somewhat less among those inoculated on the 5th day, and least in the mice inoculated immediately after X-radiation. These results show that mice are most susceptible to bacterial invasion during the 2nd week following radiation.

Failure of which antibacterial defenses is re-

sponsible for invasion by intestinal bacteria? The destruction of the intestinal mucosa is not the responsible factor, since it occurs very early after irradiation and is found to be repaired (19) at the time when the animals are most susceptible to invasion by intestinal microorganisms. A study of the passage of intestinal bacteria through the gut by Gordon *et al.* (20) showed that intestinal bacteria can be cultured from the mesenteric lymph nodes in about 50 per cent of normal mice; however their livers, spleens, and blood are generally sterile.

In irradiated animals the liver and spleen are already infected on the 3rd day, and about 48 hr later intestinal organisms can be cultured from the blood, suggesting a progressive failure of the reticulo-endothelial system's ability to suppress the bacteria.

Can the increased susceptibility of irradiated animals be explained by the failure of any single anti-infectious mechanism? Normal defenses against infection depend upon several factors: polymorphonuclear leucocytes, antibodies, bactericidal power of serum, and the reticulo-endothelial system. However, the degree to which the function of any of these systems is critical for a favorable outcome depends to a great extent upon the infective agent and the source of the infection.

How are each of these mechanisms affected by X-radiation damage? The effect of X-radiation on the antibody response in relation to resistance to infection has been extensively reviewed by Talmage (21). Dixon (22), Taliaferro (23), and their associates have observed that the primary immune response is very sensitive to moderate doses of X-radiation if the antigen, either soluble or particulate, is administered from 12 hr to 21 days after irradiation. If the antigen is administered from 4 days before to 6 hr after irradiation, antibody formation is only slowed. With respect to resistance to infection with intestinal organisms, one is more concerned with the secondary immune response. Dixon *et al.* (22) find the secondary response to a soluble antigen relatively radioresistant, while Taliaferro observed that it is very radiosensitive if particulate antigens such as sheep red blood cells are used. In view of the very small level of antibody required for maximal opsonization (24), or killing of bacteria (25) by serum, it seems doubtful that the deficiency in antibody response plays the predominant role in postradiation spontaneous infections. Numerous studies have been made of serum components involved in bactericidal action after X-radiation. Marcus and Donaldson (26) and Fishman and Shechmeister (27) agree that in rabbits and rats there is a marked loss of bactericidal property of the serum in the first week after irradiation. However, natural agglutinins to sheep red cells and *Bacillus subtilis* are unchanged at this time, and complement levels were of the same magnitude in controls and in irradiated rabbits (28). Pillemer and his group (29) confirmed that complement components in serum are not depressed in rats subjected to 500 r but observed a drastic fall in properdin level during the early postradiation period. They attributed the lack of bactericidal power of the serum to this deficiency.

Circulating polymorphonuclear leucocytes decrease markedly in the postradiation syndrome and return slowly to normal levels. Moreover, the available leucocytes were found by Shechmeister and Fishman (30) to show depression in migration, most marked on the 3rd to 5th days and again on the 10th to the 13th days.

Since the experiments of Chrom (4) and of Miller and his group (20) suggested that in irradiated animals the reticulo-endothelial system (RES) is unable to maintain the sterility of the blood, considerable work has been done to investigate the phagocytic and proliferative capacity of the RES and the ability of its macrophages to digest phagocytized material and to kill phagocytized bacteria in X-irradiated animals.

On the basis of histological evidence (31, 32) the macrophages of the RES have been found to be radioresistant. Experiments concerned only with the distribution of phagocytized material after intravenous injection provide only limited information on the phagocytic activity of the RES, since the primary change reported, a decrease in uptake by the spleen after heavy doses of X-ray observed by Gyi and Marcus (33), may be compensated by the phagocytic activity of the Kupffer cells and may merely reflect the reduction in size of this organ. Most authors investigating phagocytic function have reported that the clearance of colloidal particles from the blood by the RES is unaffected by whole body X-irradiation. However, these early studies (34–37) were carried out with very small doses of radioactive colloidal tracers, which are cleared

very efficiently and very rapidly by the Kupffer cells. These were never administered in dosage sufficient to challenge the phagocytic capacity of all the cells of the RES. The phagocytic function of the RES can be explored only when a sufficient dose of particles is injected to challenge all the phagocytic cells. In this range, the rate of clearance from the blood of an homogeneous suspension follows an exponential function of the time and varies inversely with the dose injected (38).

Studies on blood clearance of carbon particles by the RES have shown that 600 r to mice or 850 r to rats (LD_{50} range) did not interfere with the ability of the RES to clear colloidal particles from the blood (39). An LD_{100} dose of 1000 r to mice decreased the rate of clearance of carbon, but the mice were in such poor condition that some doubt was raised as to the significance of this effect on the RES. Whereas an LD_{50} dose of X-radiation does not affect the phagocytic activity of the RES, it does inhibit the recovery of its normal phagocytic function after blockade with carbon. Exposure to X-rays also suppresses the increase in phagocytic activity observed after the injection of zymosan in mice (39). These two phenomena, the return of normal phagocytic activity after blockade and the stimulation of phagocytic function by zymosan, have been shown to depend upon the proliferation of macrophage elements of the RES (40, 41). It is not surprising, therefore, that these processes are susceptible to ionizing radiation in the light of the observation of Puck on irradiated pure cell lines (42). The RES normally reacts rapidly to stimulation by cellular proliferation in animals that respond favorably to infections (43, 44). The loss of this defense reaction following irradiation may in part account for the greater susceptibility to infection of irradiated animals.

The clearance of bacteria, especially gram-negative intestinal organisms, from the blood by the RES is a much more complex process than the clearance of colloidal particles, because the extent of opsonization by antibody and complement (B. Benacerraf and P. Miescher, *unpublished data*) affects the efficiency of clearance by the liver and spleen. The data reported by various groups of investigators (24, 45–47) show that the RES phagocytes of irradiated (600 to 800 r) rats, mice, or rabbits are able in a first stage to clear live or dead bacteria from the blood as efficiently as the RES of normal animals. In irradiated rabbits, Calloway and Kerby (48) found the efficiency of splanchnic removal of staphylococci to be around 70 per cent, just as in control animals. However, Miller and co-workers (47) observed that in irradiated rabbits the colony count of intravenously injected *Klebsiella pneumoniae* increased steadily in the blood from 8 hr after inoculation until death. It seems, therefore, that although the RES of irradiated animals is able to clear bacteria from the blood, it is unable to kill them or retain them. The work of Nelson and Becker (49, 50) demonstrates very clearly the deficiency of the fixed and wandering macrophages of irradiated animals. Making use of a very ingenious technique, these investigators provoked peritoneal exudates in mice by the injection of gelatin 5 days postirradiation. *Pseudomonas aeruginosa* was then injected intraperitoneally. After allowing time for phagocytosis, polymyxin B was injected to kill all extracellular organisms. Then the cell suspension was harvested, washed, and incubated *in vitro* in tissue-culture medium for several hours, while samples for colony counts were removed. The amount of cellular exudate recovered was significantly decreased in irradiated animals. These studies established also that the macrophages from irradiated animals were not able to kill the phagocytized bacteria. If the mice had been immunized before irradiation, their phagocytes destroyed intracellular pseudomonads much more rapidly than did phagocytes from nonimmunized mice. Before interpreting this finding as the result of a specific immune mechanism, it should be controlled with endotoxins in view of the favorable effects reported with these bacterial products on infection and X-radiation damage.

Nelson and Becker (50) showed also that phagocytized bacteria lived and multiplied in the liver and spleen of X-irradiated mice. What deficiencies exist in the macrophages of irradiated mice, which allow for bacterial multiplication of normally avirulent organisms? The answer to this question depends upon our knowledge of the mechanism by which macrophages kill phagocytized bacteria, of which not much is known. To consider that bacteria are killed within macrophages by simple digestive processes, analogous to proteolysis, appears grossly oversimplified. Donaldson and associates (51) have shown that chicken red cells are digested less readily by peritoneal phagocytes of irradiated rabbits than by

those of unirradiated animals. On the other hand, Benacerraf *et al.* (39) failed to observe any change in the ability of the liver Kupffer cells of irradiated animals to metabolize heat-denatured I^{131}-labeled serum albumin and release the label.

The level of proteolytic enzymes in Kupffer cells does not seem to be affected by X-radiation. One would expect only those cellular components which have a fast turnover or which are synthesized adaptatively to be sensitive to the dosage of radiation used. This suggests that the cellular substances involved in the destruction of bacteria by macrophages are of such nature.

Further knowledge of the relationship between macrophages and phagocytized bacteria will allow a better understanding of both damaging effects of X-rays and protective effects of endotoxin (52) or mycobacteria (53).

Some agents besides antibiotics, which protect against the damaging effects of X-radiation on antibacterial defenses, remain to be mentioned. The beneficial effect of spleen homogenates and spleen shielding has been well investigated by Jacobson and his associates (54).

More recently, Smith and co-workers (55, 56) and Zweifach and associates (57) have observed independently that previous treatment with endotoxins afforded a considerable degree of protection against the mortality due to X-irradiation. Their observations relate this protection to an effect on the stem cells of the RES, to a faster repopulation of the bone marrow, and to a more rapid return of blood platelets to normal.

In view of the effects of endotoxin on resistance to infection and on the RES, these factors may also be involved in the favorable effects of pretreatment with lipopolysaccharides in X-irradiated animals.

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DISCUSSION

Irradiated mice do not ordinarily show a secondary immune response and the rate of clearance of gram-negative bacteria (*Escherichia coli*) from the blood is poor, but the phagocytic activity of the reticulo-endothelial system can be increased by passive immunization with antiserum. This fact suggests that the ability of the animal to produce antibody is seriously impaired by irradiation whereas the phagocytic activity of the fixed macrophages may be unaffected (Rowley, England).

Destruction of intracellular bacteria by macrophages from immunized, irradiated animals is more effective than by macrophages from nonimmunized animals. This increased destruction of microorganisms by phagocytes from immunized animals cannot be duplicated by phagocytes from nonimmunized animals even when the bacteria are treated with specific antibody prior to phagocytosis. The mechanism of this enhanced activity of cells from immunized irradiated animals is obscure, but the observations suggest that serum factors alone are not responsible for the enhanced cellular activity (Nelson, California).

Recent studies have shown that bacteria can actively metabolize not only serum protein and other substrates but also the monocytes that have phagocytized them, and no evidence to date has shown that cells from nonimmunized animals influence the metabolism of the bacteria, although monocytes from immunized animals do have this ability and appear to be less susceptible to the effects of the bacteria (Nelson, California).